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Article (Accepted Version)

Lam, Matthew, Commandeur, Daniel, Maniruzzaman, Mohammed, Tan, Deck Khong and Nokhodchi, Ali (2020) The crucial effect of water and co-solvent on Liqui-Pellet pharmaceutical performance. *Advanced Powder Technology*, 31 (5). pp. 1903-1914. ISSN 0921-8831

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Contents lists available at ScienceDirect

Advanced Powder Technology

journal homepage: www.elsevier.com/locate/apt

Original Research Paper

The crucial effect of water and co-solvent on Liqui-Pellet pharmaceutical performance

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ARTICLE INFO

Article history:

Received 27 September 2019

Received in revised form 20 January 2020

Accepted 20 February 2020

Available online xxxxx

Keywords:

Liqui-Pellet

Liqui-Mass system

Pellets

Liquisolid

Dissolution rate

Load factor

Liquid vehicle

ABSTRACT

Liqui-Pellet is considered to be the next generation oral dosage form. It is highly commercially feasible unlike its predecessor, liquisolid formulation. Liqui-Pellet uses Liqui-Mass system, allowing the formulation to overcome some of the critical drawbacks in liquisolid technology, which persisted more than two decades. These drawbacks include poor flowability, poor compressibility and inability for high dose without product being too heavy and bulky for swallowing. The investigation is an extension of the previous work on the Liqui-Pellet. In order to make this novel oral delivery system a commercial product, it is prudent to further understand the parameters affecting its drug release rate. Two major parameters affecting the dissolution rate that is investigated are water and liquid vehicle (Tween 80) contents. It is found out that reducing water content (from 8.62 ml to 4.76 ml which is 1.9 ml/0.95 ml per 20 g of API and excipients) and increasing Tween 80 concentration (from 28% w/w to 32 or 36% w/w) in naproxen Liqui-Pellet results to an increase in drug release rate; however, there is a limit of how much water and Tween 80 can be employed. Outside of this range limit, the formulation would fail to produce Liqui-Pellet due to agglomeration. The range limit of granulation liquid and liquid vehicle content are dependent on one another. In the successful formulation where Liqui-Pellets are formed, the excellent-good flow properties, resistant to friability and narrow size distribution makes it ideal for commercial production. SEM of the Liqui-Pellet shows a smooth surface which is ideal for coating. The solid state analysis via XRPD and DSC indicated reduced crystallinity of the drug which is expected.

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1. Introduction

It is well known that there are many water insoluble drugs facing a critical drawback of poor bioavailability, either in the market or in the development pipeline. The poor bioavailability is typically due to poor drug dissolution rate. It is stated that around 60% of drugs in the market and 40% of drugs in the development stage are poorly water-soluble [1].

In brief, Liqui-Pellet could be considered the next generation oral dosage form, stemming from liquisolid concept and pelletization technologies [2,3]. It should be made clear that Liqui-Pellet is different from liquisolid pellet. Liquisolid pellet was first reported by Pezzini et al. using the classical liquisolid system [4]. Liqui-Pellet is

essentially different compared to liquisolid technology where the former uses Liqui-Mass system instead of liquisolid system. This essentially means that the mixture of active ingredient and excipients is not essentially a free-flowing powder, but instead can be a wet mass or paste. The formulation only becomes free-flowing powder when the wet mass is transformed into the pellet form using extruder/spheroniser. Due to this key difference, the new dosage form is called Liqui-Pellet and not liquisolid pellet.

In studies by the authors, Liqui-Pellet has shown remarkable potential for increasing drug release rate, whilst overcoming the drawbacks of the classical liquisolid technology [2,3]. The key drawbacks of the classical liquisolid formulation are poor flowability, poor compressibility and incapable of producing high dose drug in an acceptable size and weight [5,6]. Liqui-Pellet on the other hand, can achieve excellent-good flow properties with high liquid load factor without compromising the inherent advantages of liquisolid technology as shown in the authors previous studies [2,3].

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Liqui-Pellet has a range of inherent advantages, making it uniquely different and desirable compared to other drug dissolution enhancing technologies. Unlike a lot of current technologies, Liqui-Pellet can hold all three major advantages of being simple, cost-effective and safer due to more predictable drug release and absorption [5,6]. Additionally, it uses green technology and may potentially resolve issues with polymorphism if API kept in a liquid state. The incorporation of a high amount of liquid medication whilst having the ability to achieve excellent flowability and the potential for versatile modification makes Liqui-Pellet an exciting and interesting dosage form. The high liquid load factor can potentially make high dose Liqui-Pellet formulation without becoming too bulky. It is in fact thought to be potentially highly commercially feasible unlike its predecessor [2,3].

There are additional advantages in having the formulation in a pellet form. Pellet form reduces the risk of dose dumping and small uniform size of pellets allows a more predictable drug dispersion and transportation in the gastrointestinal tract (GIT) [7]. The small size of the pellet allows better distribution in the GIT, which could improve bioavailability due to better drug absorption. Furthermore, since drug is freely distributed in the GIT, there is reduced risk of high drug concentration at the local site; thus, risk of toxicity and side effects can be reduced [8]. Also, there is less variation in gastric emptying; hence inter and intra variability of plasma drug profile is minimized, reducing the risk of side effects [9,10].

Among the pelletization technique, extrusion-spheronization is the chosen technique for this study. This is because it has a major advantage in that it is capable of having high loading of API without producing very large particles [11,12]. The API is integrated within the pellet structure unlike some pelletization technique where the API is only present at the surface of the pellet. In addition, the extrusion-spheronization technique can produce pellets with uniform size, good flowability, narrow size distribution and smooth surface [11].

Our previous study showed that naproxen Liqui-Pellet is able to achieve excellent flow properties (in accordance to Carr's compressibility index and angle of repose) with a load factor of 1.52 (this is considered very high value) where 38% of total pellet mass contains liquid vehicle [2,3]. Initially, in the early studies, naproxen Liqui-Pellet has high liquid load factor and excellent flowability but the drug release rate is slow (~17% release after 2 h at pH1.2) [2]. This is due to the use of microcrystalline cellulose (MCC) as a carrier. MCC-based pellet produced from extrusion-spheronization is known to form a strong bond, which renders it virtually non-disintegrating [13,14]. It is later found that this inability to disintegrate is the drug release rate-limiting step in Liqui-Pellet [2,3]. Modifications of the formulation are later carried out and it is found that water content incorporated in extrusion-spheronization is the key in determining Liqui-Pellet propensity to disintegrate [3]. In addition, the amount of co-solvent used in the formulation was observed to have an impact in disintegration and drug release rate [2]; thus, it seems prudent to investigate the water and co-solvent content parameters.

Water content is a crucial factor in a formulation containing MCC; this is to achieve good rheological properties for a successful pellet production via extrusion-spheronization [15]. Moisture content affects the internal porosity, friability, mechanical strength/cohesiveness, particle size distribution, shape and size of the pellets [16,17]. In studies by Otsuka *et al.*, an increase in water content results to increase hardness, which effectively reduces friability due to the decrease of internal porosity of pellets [18]. Non-volatile co-solvent such as Tween 80 has a plasticizing effect [19], which can result in pellets with a better plastic property because of the polymer transit from glassy to rubbery state [20].

In this study, the key objective is to observe the drug release profile of Liqui-Pellet formulation made from varying water and

co-solvent content. The study begins with investigating the most suitable co-solvent among Tween 20, Tween 80 and Tween 85. Afterwards, the water content will be varied in different formulations to observe its effect on the drug release profile. Then the specific effect of varying water and co-solvent content will be investigated. With further understanding of the effect of drug release of the mentioned parameters, it is possible to control and tailor the dissolution behaviour of Liqui-Pellet.

2. Materials and methods

2.1. Materials

Naproxen API was obtained from Tokyo Chemical Industry Co (Japan). Other materials involved in the Liqui-Pellet production included Avicel PH-101 (FMC corp., UK); Aerosil 300 (Evonik, Germany); sodium starch glycolate Type A as superdisintegrant (Primojel from DFE Pharma, Germany); polysorbate 20 liquid vehicle (Tween 20), (Acros, Netherlands); polysorbate 80 liquid vehicle (Tween 80), (Acros, Netherlands) and polysorbate 85 liquid vehicle (Tween 85), (Acros, Netherlands). All other reagents and solvent were of analytical grades.

2.2. Saturation solubility studies

Saturation solubility test of naproxen in 3 different non-volatile co-solvents (Tween 20, Tween 80 and Tween 85) were carried out. Only different types of Tween were used as previous studies showed Tween 80 being the most suitable liquid vehicle among polyethylene glycol 200, propylene glycol, Labrafil, Labrasol and Kolliphor EL [2]. Excess naproxen powder was added into glass vials containing 10 ml of liquid vehicle. The vials containing saturated naproxen in a specified liquid vehicle were then placed in a bath shaker (OLS Aqua Pro, Grant Instruments Ltd, UK). The samples were agitated under the shaking at a speed of 40 rpm for 72 h. Thereafter the sample's supernatant was drawn out of the vial using a syringe and then filtered through a pre-heated filter (Millex syringe filter with pore size of 0.22 μm). The filtrated sample was then diluted with phosphate buffer solution (pH 7.4) followed by determination of API using UV/vis spectrophotometer analysis (Biochrom Ltd, UK) at a wavelength of 271 nm. Each test was carried out in triplicates.

2.3. Preparation of naproxen Liqui-Pellet with different Tween co-solvent

The preparation of Liqui-Pellet was made in a similar manner to the authors' previous studies [2,3]. The preparation includes naproxen being mixed with a specified liquid vehicle (Tween 20, Tween 80 and Tween 85) of specified amount via pestle and mortar. All formulations in Table 1 had a ratio of carrier (Avicel PH-101) to coating material (Aerosil 300) 20:1. Avicel PH-101 was mixed into the liquid medication (naproxen and liquid vehicle) where the carrier absorbs or adsorbs the liquid medication. The mixture was transferred into a mixer (Caleva Multitab, Caleva Process Solutions Ltd, UK) followed by the addition of primojel (superdisintegrant) at a concentration around 5 %w/w. The mixer was set at a constant rate of 125 rpm for 10 min with a specified amount of granulating liquid (deionized water using SUEZ deionized water system, France) added during the process. A specified amount of Aerosil 300 was incorporated into the admixture, which underwent an additional 10 min mixing. Thereafter the Liqui-Mass composition was extruded (125 rpm) and spheronized at 4000 rpm, but may be adjusted between 2500 rpm and 4500 rpm to avoid agglomeration or improve sphericity. Note that the duration of

Table 1

Key formulation characteristics of the investigated Liqui-Pellet capsule.

Formulation	Water content during extrusion-spheronization (ml) per 20 g of admixture of API and excipient	Amount of liquid vehicle (% w/w)	Type of liquid vehicle	Liquid load factor	Mass of carrier (mg)	Mass of coating material (mg)	Successfully spheronize into pellets? (Yes/No)	Total weight of 25 mg naproxen Liqui-Pellet (mg)
Physical mixture pellet	6.01	–	–	–	58.15	2.90	Yes	90.58
LP-1	8.62	28	Tween 20	1	62.41	3.11	Yes	132.70
LP-2	8.62	28	Tween 80	1	62.41	3.11	Yes	132.70
LP-3	8.62	28	Tween 85	1	62.41	3.11	Yes	132.70

Note that all formulation contained 25 mg of naproxen, Primojel 5% w/w and the carrier to coating ratio of 20:1 respectively.

spheronization process varied for each formulation, which was dependent on factors such as extrudate plastic property, pellet sphericity and risk of agglomeration. Next, the samples were dried overnight using an oven (40 °C). Details of each formulation composition are shown in Table 1.

2.4. Preparation of naproxen Liqui-Pellet with varying water content and co-solvent concentration

The Liqui-Pellet formulations in Table 2 were prepared in a similar manner as the formulations in Table 1; however, the water content and the amount of co-solvent added varied as shown in Table 2. The ratio of carrier to coating material for all formulations was 20:1. Note that not all formulations were successfully made as agglomeration occurred during the spheronization process.

2.5. Evaluation of formulated Liqui-Pellet

2.5.1. Flowability test on formulated Liqui-Pellet

Flow rate, angle of repose and Carr's compressibility index were determined for all formulations. This is done in the same manner as in the authors' previous work [1,2]. All successful measurements were done in triplicates. The following equations were used to calculate the angle of repose and Carr's Index:

Angle of repose

$$= \tan^{-1}(\text{height of heap of sample} / \text{radius of heap of the sample}) \quad (1)$$

$$\text{CI\% (Carr's Index)} = (\rho_t - \rho_b) / \rho_t \times 100 \quad (2)$$

Table 2

Key formulation characteristics of the investigate Liqui-Pellet capsule.

Formulation	Water content during extrusion-spheronization (ml) per 20 g of admixture of API and excipient	Amount liquid vehicle (% w/w)	Type of liquid vehicle	Liquid load factor	Mass of carrier (mg)	Mass of coating material (mg)	Successfully spheronize into pellets? (Yes/No)	Total weight of 25 mg naproxen Liqui-Pellet (mg)
LP-4	8.57	32	Tween 80	1.18	57.57	3.88	Yes	132.70
LP-5	8.57	36	Tween 80	1.38	52.77	2.64	No	132.70
LP-6	8.57	40	Tween 80	1.63	47.96	2.40	No	132.70
LP-7	8.57	44	Tween 80	1.94	43.16	2.16	No	132.70
LP-8	4.76	32	Tween 80	1.18	57.57	3.88	Yes	132.70
LP-9	4.76	36	Tween 80	1.38	52.77	2.64	Yes	132.70
LP-10	4.76	40	Tween 80	1.63	47.96	2.40	No	132.70
LP-11	4.76	44	Tween 80	1.94	43.16	2.16	No	132.70
LP-12	1.90	32	Tween 80	1.18	57.57	3.88	Yes	132.70
LP-13	1.90	36	Tween 80	1.38	52.77	2.64	Yes	132.70
LP-14	1.90	40	Tween 80	1.63	47.96	2.40	No	132.70
LP-15	1.90	44	Tween 80	1.94	43.16	2.16	No	132.70
LP-16	0.95	32	Tween 80	1.18	57.57	3.88	Yes	132.70
LP-17	0.95	36	Tween 80	1.38	52.77	2.64	No	132.70
LP-18	0.95	40	Tween 80	1.63	47.96	2.40	No	132.70
LP-19	0.95	44	Tween 80	1.94	43.16	2.16	No	132.70

Note that all formulation contained 25 mg of naproxen, Primojel ~5% w/w and the carrier to coating ratio is 20:1 respectively.

where ρ_b being the poured density and ρ_t being the tapped density.

2.5.2. Friability test on formulated Liqui-Pellet

The method of friability test was the same as the authors' previous friability studies [2,3]. This method adapted a similar method that was used in Hu studies [21], with additional modification such as sealing the friabilator to prevent pellets from leaving the container. Specified sample of Liqui-Pellets weighing 3 g in total and glass beads also weighing 3 g in total were placed in a friabilator (D-63150, Erweka, Germany). The friabilator was set to 100 rotations in 4 min. The percentage weight loss of the formulation was determined by means of the weight of the pellets prior to and after the friability test.

2.5.3. Particle size analysis via sieve method

The distribution of particle size was determined using sieves method (Test sieve, Retsch, Germany). All formulations that were successfully extruded and spheronized were tested. Specified sample of Liqui-Pellet (5 g) was sieved via a mechanical shaker (AS 200, Retsch, Germany), which was set at an amplitude of 60 for a minute then the amplitude of 40 for 9 min. Sieve size used were 2000, 1000, 850, 500, 250 μm . The Liqui-Pellet yield in percentage was then determined.

2.5.4. Scanning electron microscope (SEM) analysis

The surface morphology of the Liqui-Pellet formulations was studied using SEM (Jeol JMS 820, Freising, Germany). Each sample was placed in double-sided carbon tape and sputter-coated with gold using a sputter coater with gold target and Argon gas under 5 kV for 5 min. Once coated the samples were placed into the SEM machine (operating at 3 kV) where the surface structure was investigated at magnifications of $\times 80$ and $\times 800$.

2.6. In-vitro dissolution test

The dissolution tests were carried out in a similar manner as in the authors' previous publication on naproxen Liqui-Pellet [2,3]. USP paddle method (708-DS Dissolution Apparatus & Cary 60 UV-Vis, Agilent Technologies, USA) was the chosen dissolution test method. The dissolution medium used were either 900 ml of HCl buffer solution (pH of 1.2) or 900 ml phosphate buffer solution (pH of 7.4). The temperature was set at $37.3 \pm 0.5^\circ\text{C}$ and paddle agitation at 50 rpm. Absorbance was set at 271 nm and samples were taken at different time intervals of 5 min until 1 h then time interval of 10 min for another hour.

Dosage of 25 mg of naproxen was used for all dissolution tests, mainly because naproxen has poor solubility profile under acidic environment (i.e. pH 1.2). This is due to naproxen weak acidic properties, where it is well known that acidic APIs are usually insoluble in an acidic environment but soluble in a basic environment. According to studies by Mora and Martinez [22], naproxen solubility at 35°C and pH 1.2 was 1.16×10^{-4} mol/L or 27 mg/L; hence, 25 mg were chosen as a reasonable amount of drug for this test. For convenience, 25 mg of naproxen were also used at pH 7.4. Although at pH 1.2, the sink condition was not maintained, the key purpose was to compare the various formulations.

2.7. Differential scanning calorimetry (DSC) and X-ray powder diffraction (XRPD) studies

DSC and XRPD were performed on excipients, naproxen and all successful formulations to assess their crystallinity. For DSC (DCS 4000, Perkin Elmer, USA), between 3 and 6 mg of sample were weighed and sealed in an aluminium pan. The thermal behaviour, which correlates to the crystallinity, was investigated at a scanning rate of $10^\circ\text{C}/\text{min}$, from 25°C to 200°C under nitrogen atmosphere.

X-ray diffractometer (D5000, Siemens, Germany) was used to analyze the samples with scanning angle ranged from 5° to 40° with a scan rate of $0.02^\circ/\text{s}$. Voltage and current were set to 40 kV and 30 mA respectively. The relative crystallinity of the sample was determined using the integrated peak method (Eq. (3)) and peak height method (Eq. (4)) [23]. For integrated peak method, the area under the curve was calculated using the trapezoid method.

$$\% \text{ XRD relative crystallinity} = (A_s/A_r) \times 100 \quad (3)$$

$$\% \text{ XRD relative crystallinity} = (H_s/H_r) \times 100 \quad (4)$$

2.8. Mathematical analysis

Data from the dissolution studies were mathematically analyzed using difference factor (f_1) equation Eq. (5) and similarity factor (f_2) equation Eq. (6) as described by Moore and Flanner [24]. The US FDA (Food and drug administration) recommended these mathematical analyses for comparing dissolution profiles recommended [25], which have been included in various guidance documents issued by the FDA [26,27]. Difference factor with a value between 0 and 15 and similarity factor with a value between 50 and 100 indicates equivalence of the two dissolution profiles [28]. Details of the equations can be found in various literature [25,29–31]; however, in general, n represents the number of dissolution sample times and R_t & T_t represent the mean % of drug dissolved at each time point (t).

$$f_1 = \left\{ \left[\sum_{t=1}^n R_t - T_t \right] / \left[\sum_{t=1}^n R_t \right] \right\} \cdot 100 \quad (5)$$

$$f_2 = 50 \cdot \log \left\{ \left[1 + (1/n) \sum_{t=1}^n (R_t - T_t)^2 \right]^{-0.5} \cdot 100 \right\} \quad (6)$$

3. Results and discussion

3.1. Saturation solubility studies

Results from the saturation solubility study (Table 3) shows naproxen is sparingly soluble in Tween 20, Tween 80 and Tween 85. Among the mentioned Tween liquid vehicles, which are non-ionic surfactant derived from sorbitan ester [32], naproxen has the highest solubility in Tween 80 (21.85 mg/ml) and least soluble in Tween 85 (14.27 mg/ml). This agrees with data from the dissolution studies where Tween 80 has the highest drug release rate and Tween 85 is the slowest. T-test was performed to compare the significance of the solubility data and the results showed that although Tween 80 showed the highest solubility the difference in the solubility between Tween 80 and Tween 20 was not significant ($p > 0.05$), but the difference was significant when compared

Table 3
Solubility of naproxen Liqui-Pellet in Tween 20, 80 and 85 at 37°C ($n = 3$).

Non-volatile solvent	Mean concentration (mg/ml) \pm SD ^a	Inference
Tween 20	17.98 ± 3.09	Sparingly soluble
Tween 80	21.85 ± 1.88	Sparingly soluble
Tween 85	14.27 ± 1.58	Sparingly soluble

^a SD, standard deviation from the mean

to the solubility of naproxen in Tween 85 ($p > 0.05$). The general assumption is that the formulation containing the liquid vehicle that the API is most soluble in, would have the fastest drug release rate. The increase in the dissolution rate could be as a result of increasing the surface area of API in the formulation due to the presence of solubilised form or molecularly dispersed form of API [33].

The differences in the solubility in various Tweens are due to their different properties; however, the detailed explanation remains unclear. On comparing the HLB (hydrophilic-lipophilic balance), Tween 20 (HLB = 16.7) have the highest HLB followed by Tween 80 (HLB = 15.0) then Tween 85 (HLB = 11.0) [34]; however, these HLB value does not seem to show a clear correlation with the solubility data or results from the drug release rate. This reinstates how predicting solubility is complex and require consideration of additional factors such as viscosity, polarity, chemical structure and molecular mass may affect drug release [6].

3.2. Success of spheronizing formulation

Not all formulations were successfully spheronized into pellets. Tables 1 and 2 show which formulations were successful and which failed in producing pellets. In general, there seems to be a limit of how much water and the liquid vehicle can be added until the formulation is prone to agglomeration, leading to failure in Liqui-Pellet production.

Within the spectrum of water content used in this investigation, 8.62 ml of water (per 20 g of API and excipients admixture) is considered high water content. At this water content, only the lowest spectrum of co-solvent (32% w/w) was able to successfully produce Liqui-Pellet. By increasing the co-solvent above 32% w/w with this high water content formulation, the extrudates produced, have cohesive surface and highly plastic properties, which lead to agglomeration during the spheronization process. It seems like there is a synergistic effect of water and Tween 80 in enhancing extrudate plastic properties. The non-ionic surfactant Tween 80 has a plasticizing effect [19] contributing to the rheology of the wet mass and extrudates. Care must be taken into consideration so that the extrudates are plastic enough to form spherical pellets when spheronized but not to the extent that would result in agglomeration.

At the mid spectrum of water content (4.76 ml and 1.9 ml of water per 20 g of API and excipients admixture), it is possible to make Liqui-Pellet with higher Tween 80 content (36% w/w). The

reason for this is because the water content is reduced, thus, the overall plasticity and cohesiveness of the extrudates do not go over the limit that can cause agglomeration. At this mid-range of water content, Tween 80 above 36% w/w, all agglomerated during spheronization process. Despite some of the extrudates appearing ideal for pellet production (i.e. short and brittle enough to break), the increased in the liquid vehicle made the extrudates' surface too cohesive that agglomeration could not be avoided.

Similar to the high spectrum of water content, the lowest spectrum of water content (0.95 ml of water per 20 g of API and excipients admixture), could only produce Liqui-Pellet successfully at low liquid vehicle concentration (32% w/w). The lack of water in the formulation affects the rheological properties of the extrudate in such that concentration of Tween 80 at 36% w/w and higher, were too soft and cohesive to be spheronized into pellets. Overall, it can clearly be seen that understanding the water and liquid vehicle limits in the formulation process is prudent for the success of producing Liqui-Pellet.

3.3. Flow properties

All successfully made formulations have shown excellent, excellent-good or good flowability (Table 4). The data from the authors' previous work also show similar results, indicating clearly that Liqui-Pellet can overcome its predecessor's (liquisolid technology) drawback of poor flow property [2,3]. This is a major step forward in bringing a concept from liquisolid technology towards a commercial direction.

Table 5
Weight loss of 3 g of each formulation under rotational speed of 25 rpm for 4 min.

Formulation	% Weight loss
Physical mixture pellet	0.14
LP-1	0.05
LP-2	0.12
LP-3	0.20
LP-4	0.29
LP-8	0.10
LP-9	0.09
LP-12	0.11
LP-13	0.29
LP-16	0.53

Table 4
Flow rate (g/sec), Angle of repose and Carr's compressible index (CI%) of all formulation (n = 3).

Formulation ^a	Flow Rate (g/sec) \pm SD ^b	Angle of repose \pm SD ^b	CI% \pm SD ^b	Inference according to Angle of repose	Inference according to CI%	Particle size distribution (%)		
						250–500	500–850	850–1000 (in μ m)
Physical mixture pellet	10.72 \pm 0.33	19.96 \pm 1.43	11.11 \pm 0.62	Excellent flowability	Good flowability	0.67	45.21	54.12
LP-1	8.77 \pm 0.16	23.81 \pm 0.74	10.08 \pm 0.55	Excellent flowability	Excellent-good flowability	64.73	32.45	3.30
LP-2	8.22 \pm 0.29	23.51 \pm 0.19	12.11 \pm 0.64	Excellent flowability	Good flowability	70.75	28.09	1.16
LP-3	8.08 \pm 0.07	23.95 \pm 0.21	12.73 \pm 0.00	Excellent flowability	Good flowability	86.28	12.50	1.22
LP-4	6.74 \pm 0.08	28.7 \pm 0.20	11.05 \pm 1.36	Excellent flowability	Good flowability	99.41	0.59	–
LP-8	7.17 \pm 0.10	27.63 \pm 0.31	10.17 \pm 0.63	Excellent flowability	Excellent-good flowability	95.45	4.38	0.17
LP-9	7.07 \pm 0.11	27.65 \pm 1.00	6.31 \pm 0.70	Excellent flowability	Excellent flowability	99.20	0.80	–
LP-12	6.12 \pm 0.18	31.02 \pm 0.66	7.33 \pm 0.00	Good flowability	Excellent flowability	98.86	1.30	0.10
LP-13	6.4 \pm 0.19	29.52 \pm 0.85	3.96 \pm 0.00	Excellent flowability	Excellent flowability	98.25	1.69	0.11
LP-16	5.57 \pm 0.25	30.87 \pm 0.55	5.80 \pm 0.74	Excellent-good flowability	Excellent flowability	98.46	1.42	0.12

^a For the composition of each formulation refer to Table 1 and Table 2.

^b SD, standard deviation from the mean.

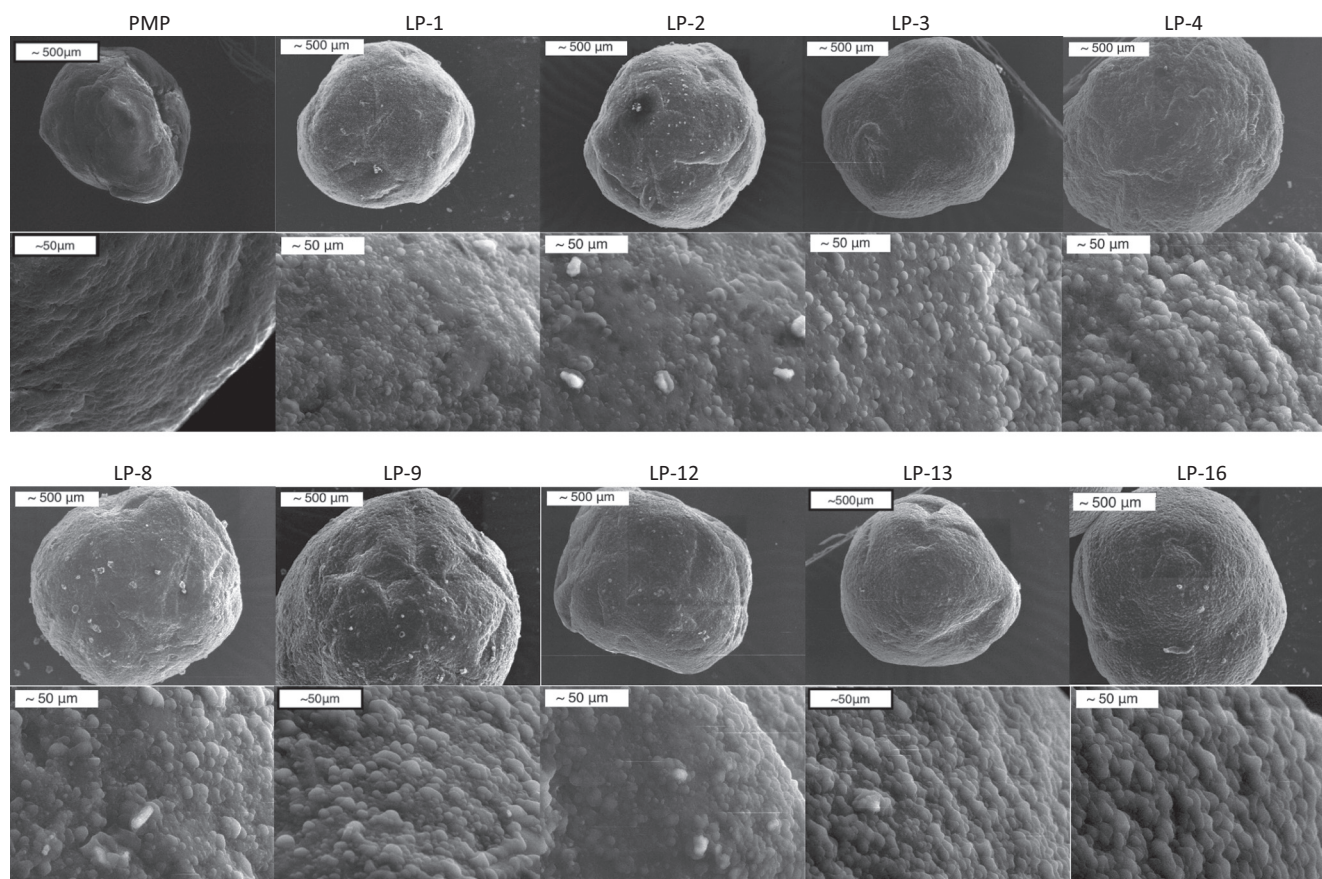


Fig. 1. SEM images of physical mixture pellet and all successful formulation under $\times 80$ magnification and $\times 800$ magnification.

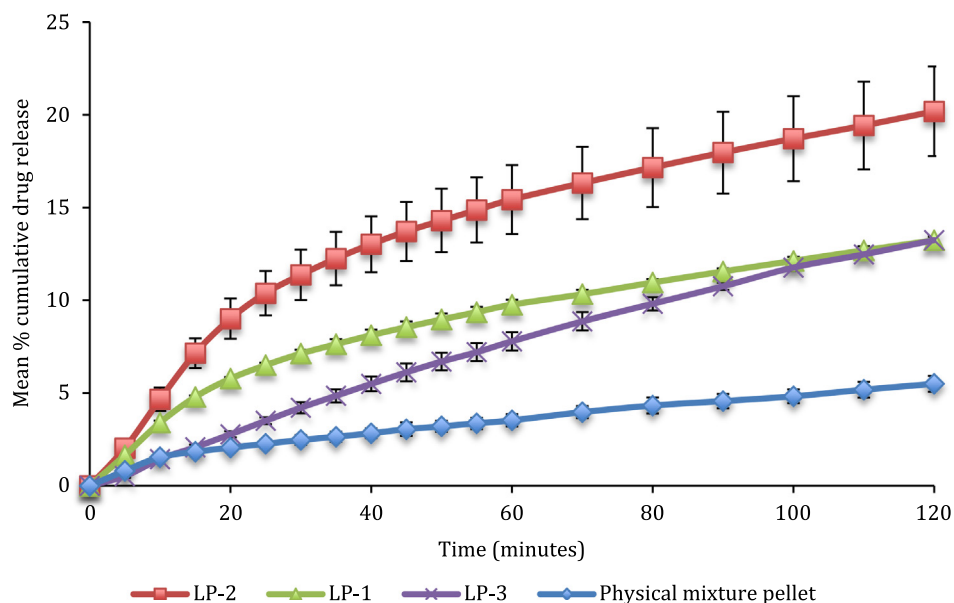


Fig. 2. Dissolution profile of 25 mg of naproxen Liqui-Pellet in capsule with different liquid vehicle (Tween 20, Tween 80 and Tween 85) and physical mixture pellet at pH 1.2.

The consistently used Tween 80 in this investigation is classified as a surfactant according to 'Handbook of Pharmaceutical Excipients' [32]. A surfactant that has high HLB value tends to reduce sharkskin effect on the extrudates, which is the result of decreased frictional force at the die wall of extrusion screen. This helps to produce pellets with higher sphericity [34]. The high

degree of sphericity contributes to the desired flow property that is evident in Table 4.

It is noteworthy to mention that some of the formulations have a liquid load factor as high as 1.38, where the total mass of pellet contains a considerable amount of liquid medication of 55%. Furthermore, since flow properties and compressibility are no longer

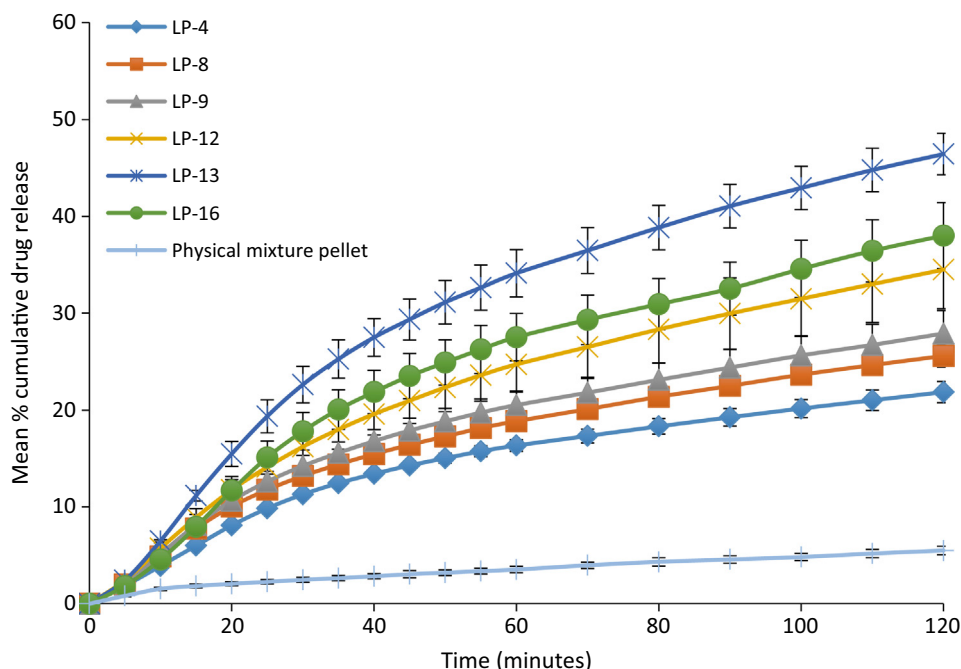


Fig. 3. Dissolution profile of 25 mg of naproxen Liqui-Pellets in capsule with different water and liquid vehicle content under pH 1.2.

a major issue in Liqui-Pellet, the production is simplified by not having to rely on the liquisolid mathematical model that was introduced by Spireas.

3.4. Friability test

All of the successfully produced formulations have a weight loss of less than 1% (Table 5), which is the limit of weight loss considered acceptable for tablet according to the USP. Liqui-Pellet formulations from the authors' previous studies also have a weight loss of less than 1% [2,3]. Presently there is no standard for friability test for pellets; however, it seems reasonable to say that the current Liqui-Pellet dosage form is robust enough in regards to commercial standard.

These Liqui-Pellets contain MCC as a carrier, which has strong bonding within its structure when water is added; in addition, the Tween 80 gives the formulation its plastic properties. Both of these enhance Liqui-Pellet resistant to friability, which is supported by the data presented in Table 5.

3.5. Particle size of formulated Liqui-Pellet via sieve method

Results obtained from the particle size analysis (Table 4), clearly shows narrow size distribution of all of the formulations apart from physical mixture pellet. Physical mixture pellets have relatively wider size distribution than the rest of the formulations ($\approx 54\%$ within 1 mm and 45.21% within 0.85 mm). This could be due to the absent of Tween 80 during physical mixture pellet production. Without Tween 80 the wet mass and extrudates would have less plastic properties, which could result in poorer pellet quality with wider size distribution.

The formulations that have exceptionally narrow size distribution are LP-4 (around 99% within 0.5 to 0.85 mm), LP-8 (around 95% within 0.5 to 0.85 mm), LP-9 and LP-12 (around 99% within 0.5 to 0.85 mm), LP-13 and LP-16 (around 98% within 0.5 to 0.85 mm) (Table 4). These narrow size distributions are ideal for commercial manufacturing, particularly when considering the uniformity of drug content during the filling process into capsules.

It is interesting how the changes in water content and Tween 80 concentration did not have a significant influence on the

Liqui-Pellet size distribution. The formulation containing 8.62 ml of water per 20 g of Liqui-Mass admixture (LP-4) and 0.95 ml of water per 20 g of Liqui-Mass admixture (LP-16) showed $\approx 99\%$ and $\approx 98\%$ within 0.5 to 0.85 mm respectively. It seems like the Tween 80 could be contributing to the reduced variability in plastic properties, consequently reducing the variability of size distribution among the formulation.

It should be noted that there are many parameters that can affect the pellet size produced from extrusion-spheronization. In brief, these key parameters include moisture content [16,17]; type and amount of granulating liquid [18]; spheronization speed, load and duration; and drying method [35]. Thus, it is actually rather difficult to be certain if parameters such as the amount of water or liquid vehicle are actually influencing the pellet size. Nonetheless, it is clear that it is possible to produce Liqui-Pellet with narrow size distribution and within the size that would allow it to have short transit time in the stomach (< 2 mm).

3.5.1. Studies of surface structure via SEM

There is a clear difference in the surface structure of Liqui-Pellet formulations and physical mixture pellet (Fig. 1). The surface of all of the Liqui-Pellet formulations has smooth round pebble-like appearance, which is not present in the physical mixture pellet (PMP). Among the different type of Tween co-solvents, Tween 20 (LP-1) shows the smallest bump size on the surface, which could suggest that the type of Tween may influence surface morphology. The rest of the formulations' surface structure looks similar to one another, with the exception of variations in bump size. It appears that LP-16 has slightly larger bumps, which protrude more than the rest of the formulations. It should be noted that the priority focus of the study is to see if it is possible to produce Liqui-Pellet with different amount of water and Tween 80 content; thus, in order to achieve this, the spheronization duration and speed were varied for optimal success rate. This may have an impact on the surface structure of the Liqui-Pellet formulations.

It is interesting to point out that in the previous study, the formulation that contained $\approx 29\%$ w/w Tween 80 did not have the smooth pebble-like appearance [2]. The pebble-like appearance

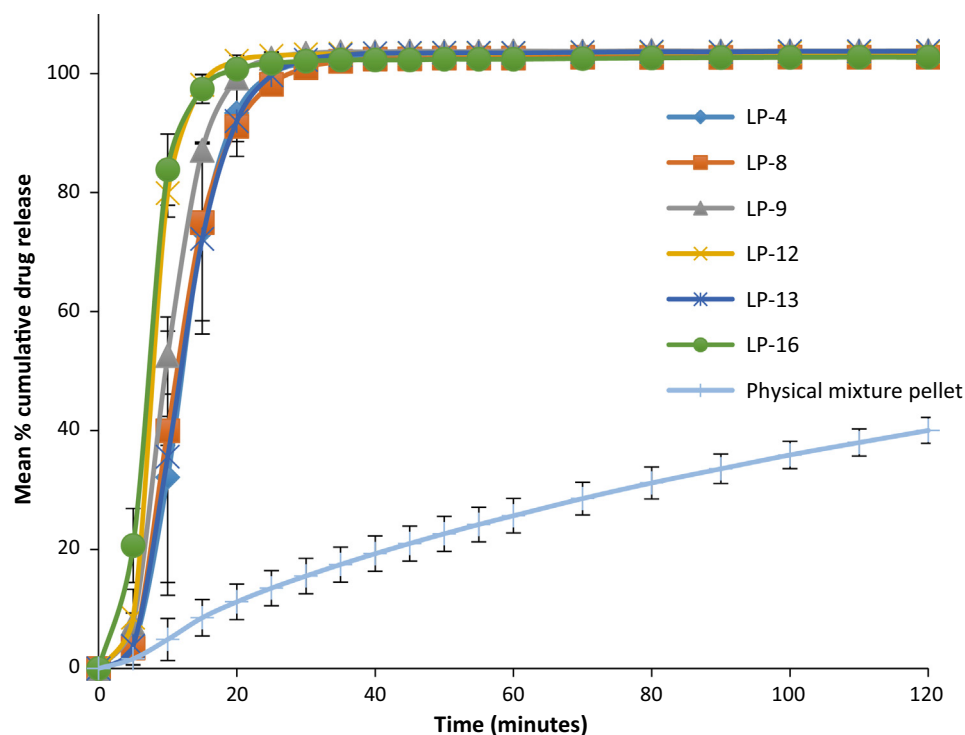


Fig. 4. Dissolution profile of 25 mg of naproxen Liqui-Pellets in capsule with different water and liquid vehicle content under pH 7.4.

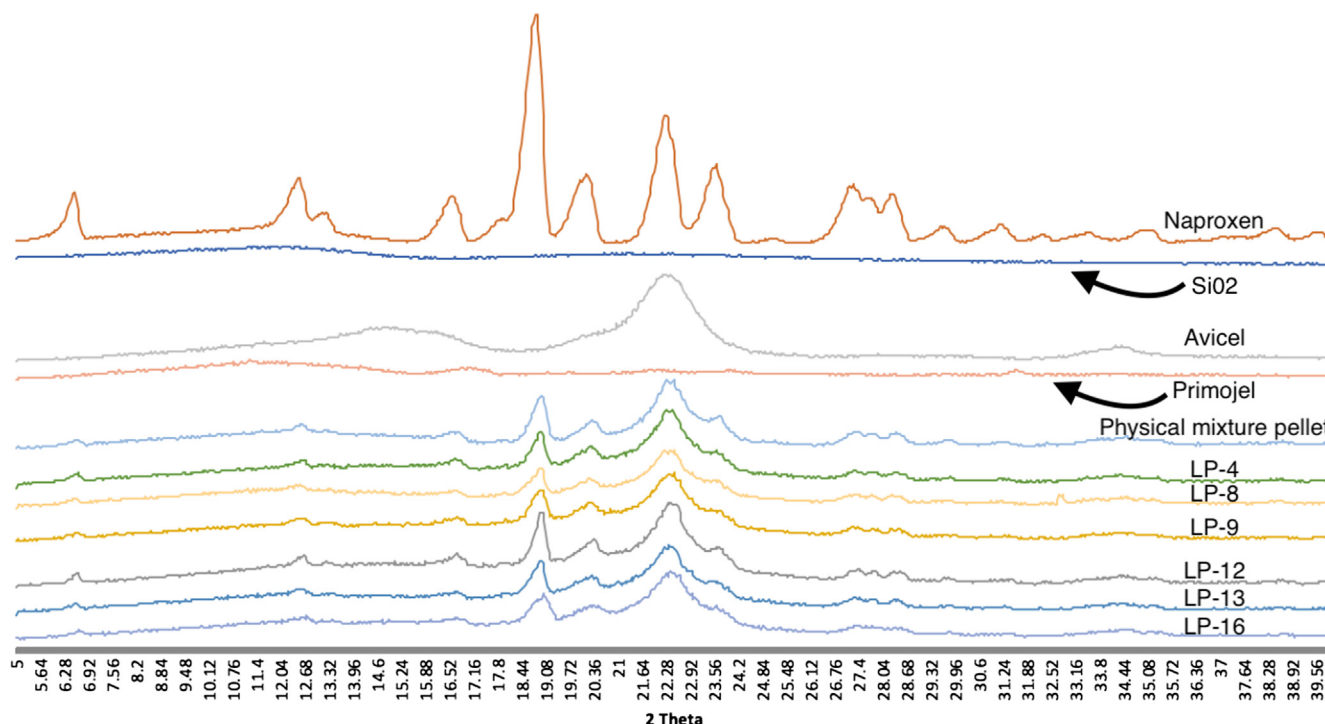


Fig. 5. Diffraction peaks of naproxen, avicel, aerosil, primojel, physical mixture pellet and all of the successful formulations.

seems to appear when the amount of Tween 80 is increased from 29% to 32% or 36% in this study.

All of the Liqui-Pellet formulations have a relatively smooth surface structure which is an important factor for successful coating [11]. The coating of these pellets is an important consideration

when making sustained and controlled release Liqui-Pellet formulation via polymeric coating. In addition, smooth surface and spherical shape of the Liqui-Pellet would make it easier to apply taste masking polymer [36–39], which may have benefits in the pediatric formulation.

3.6. Dissolution studies

Fig. 2 shows that the type of liquid vehicle used in the preparation of formulations has an impact on the dissolution rate of API where formulation containing Tween 80 showed faster drug dissolution compared to other liquid vehicles used (Fig. 2). The results correspond well to the saturation solubility studies (Table 3) in which naproxen is most soluble in Tween 80 and least soluble in TWEEN 85.

Results from Fig. 3 show the dissolution profile of all successful formulations under acidic pH of 1.2, which mimics the pH in the stomach. The figure clearly shows that the amount of water content and liquid vehicle concentration have a crucial effect on the drug dissolution profile of Liqui-Pellet. In general, a reduction in water content used in the preparation of Liquid-Pellets increases drug release rate (compare LP-4, LP-8, LP-12 and LP-16), and an increase in Tween 80 concentration increases drug release rate (compare LP-12 and LP-13).

Using mathematical analysis, it is possible to some degree to confirm that decreasing water content has an impact on the drug release rate. Formulation LP-8 (4.76 ml of water per 20 g of Liqui-Mass admixture) has an increase of $\approx 4\%$ of drug release after 2 h compared to LP-4 (8.62 ml of water per 20 g of Liqui-Mass admixture) with $f_1 = 14.54$ and $f_2 = 79.07$. Even though the f_1 and f_2 value does not show a significant difference, as the water content further decreases, it is possible to see the influences of water content on dissolution rate (Fig. 3). For example, when the water content is further decreased from 8.62 ml of water per 20 g of Liqui-Mass admixture (LP-4) to 1.9 ml of water per 20 g of Liqui-Mass admixture (LP-12), the drug release rate increased by $\approx 13\%$ after 2 h with $f_1 = 33.87$. This f_1 value shows that the dissolution rate of both of these formulations are different; LP-12 drug release rate is faster than LP-4. Furthermore, when the water content is again further decreased from 8.62 ml of water per 20 g of Liqui-Mass admixture (LP-4) to 0.95 ml of water per 20 g of Liqui-Mass admixture (LP-16), the drug release rate increased by $\approx 16\%$ with $f_1 = 39.22$ and $f_2 = 50.34$. It is clear that f_1 value is increasing and f_2 value is decreasing with decreasing water content, indicating that the drug release rate is becoming more different with changes in water content. The f_1 of 39.22 signifies the difference in drug dissolution rate of LP-16 and LP-4. It should be pointed out that the f_1 value seems to show differences in dissolution profile but not the f_2 value. It is worth stating that there seems to be no well-defined basis for the equivalence threshold of $f_2 = 50$ [25].

The enhanced drug release rate with decreased water content in the formulation can be explained in terms of MCC aggregates subunit. Sarkar and Liew state that MCC is made up of aggregates of small subunits, which are held together via hydrogen bond [40]. In order for de-aggregation of MCC subunit to occur, these hydrogen bond must be broken [40]. By taking Sarkar and Liew statement into account, when less amount of water content is used during the mixing stage, there is less polar granulating liquid to cause de-aggregation. This would lead to MCC with larger particle size. During granulation and extrusion process of this larger MCC particle size, along with less moistening liquid content, results to less surface tension and van der Waals forces; the wet mass and extrudate have reduced cohesive strength. Essentially this would produce pellets with weaker cohesive strength; thus, better propensity for disintegration, which results to faster drug release rate as disintegration is the drug release rate-limiting step for MCC-based Liqui-Pellet [2,3].

The effect of liquid vehicle content can be seen in formulation LP-12 (32% w/w Tween 80) and LP-13 (36% w/w Tween 80). Despite both having the same water content of 1.9 ml per 20 g of Liqui-Mass admixture, the difference of $\approx 12\%$ dissolution rate after 2 h is due to the different concentration of Tween 80. The $f_1 = 36.75$

indicates that LP-12 and LP-13 have a different dissolution rate; LP-13 having faster drug release rate than LP-12. Hence, Tween 80 content in the formulation does influence the drug release rate. However, the significant f_1 and f_2 values are not seen for LP-8 (32% w/w Tween 80) and LP-9 (36% w/w Tween 80) where 4.76 ml of water per 20 g of Liqui-Mass admixture is used ($f_1 = 7.64$ and $f_2 = 87.94$). It seems that Tween 80 has a greater impact on drug dissolution rate when the water content is respectively lower.

The increase in drug release rate with increasing liquid vehicle is due to more API being solubilized or in a molecularly dispersed state, which results in an increase in surface area available for dissolution [33]. This can also be explained using the Noyes-Whitney equation, where the surface area available for dissolution is directly proportional to dissolution rate [41]. In addition to the increased surface area available for dissolution, Tween 80 reduces surface tension or cohesive force, which improves propensity for disintegration; thus, further enhancing drug release rate. A similar finding in terms of Tween 80 improving disintegration of MCC-based pellet was observed by Chamsai and Sriamornsak [14].

When comparing formulation LP-4 with LP-13, the combined effect of decreased water content and increased Tween 80 shows a significant increase in drug release by $\approx 25\%$ after 2 h with $f_1 = 51.56$ and $f_2 = 40.10$. In summary, water and Tween 80 (or liquid vehicle) are crucial parameters influencing drug release rate of Liqui-Pellet. Reduced water content and increased Tween 80 improves the drug release rate of Liqui-Pellet. At the lower spectrum of water content, Tween 80 have a more prominent effect on drug release rate than at higher spectrum of water content. Nonetheless, there are limits of how much water can be reduced and how much Tween 80 can be increased. Table 2 shows which formulations failed to form Liqui-Pellets at particular water content and Tween 80 concentration, indicating the limits.

Dissolution studies at pH 7.4 (Fig. 4) show a fast drug release rate of all successfully made Liqui-Pellet formulations, which plateau at ≈ 20 min. This fast drug release rate is expected because naproxen is a weakly acidic drug, which is more soluble in alkaline pH than acidic pH environment.

3.7. XRPD studies

The diffractogram in Fig. 5 shows that naproxen peak at 2θ values of 6.4, 12.28, 12.96, 16.32, 18.72, 19.88, 22.16, 23.40, 26.96 and 28.04, which is very similar to the naproxen peak from previous studies [2,3]. The peak in physical mixture only corresponds to naproxen and Avicel, indicating that there is no interaction between API and the excipients. The physical mixture looks less crystalline than pure naproxen as the crystallinity of naproxen can be covered by the amorphousness of microcrystalline cellulose and/or excipients i.e. aerosil and primojel used in the formulation.

As XRPD of all Liquid-Pellets formulations is similar to the XRPD of the physical mixture pellet, the authors made an attempt to use

Table 6

Relative crystallinity in respect to AUC at 18.9° peak among physical mixture pellet, LP-4, LP-8, LP-9, LP-12, LP-13 and LP-16.

Formulation	% relative crystallinity via integrated peak area method	% relative crystallinity via peak height method
Physical mixture	12.92	20.27
LP-4	7.56	15.60
LP-8	4.83	11.80
LP-9	9.69	13.65
LP-12	11.54	22.17
LP-13	6.31	14.85
LP-16	6.21	12.18

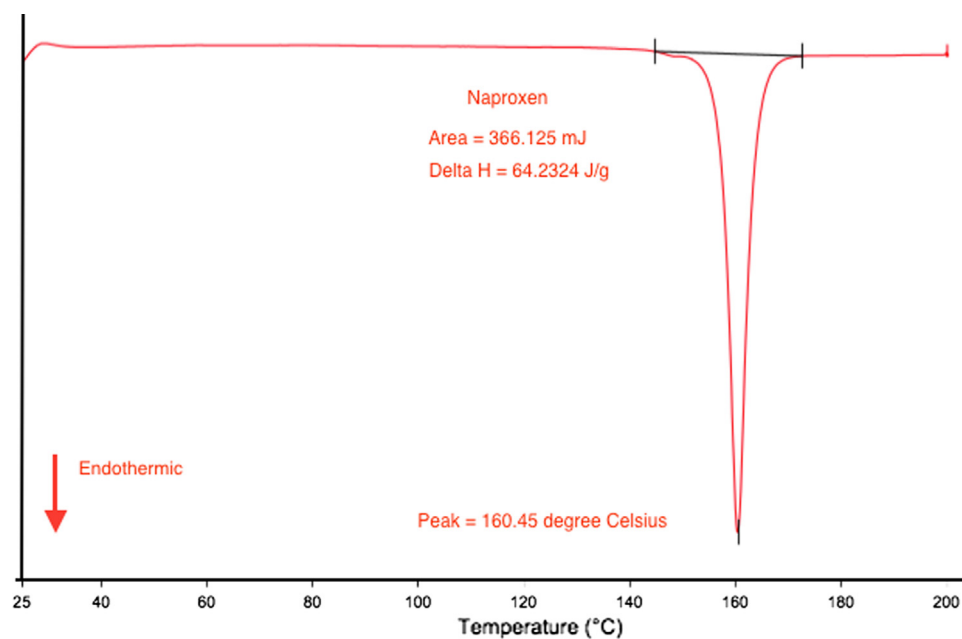


Fig. 6. DSC thermograms of naproxen.

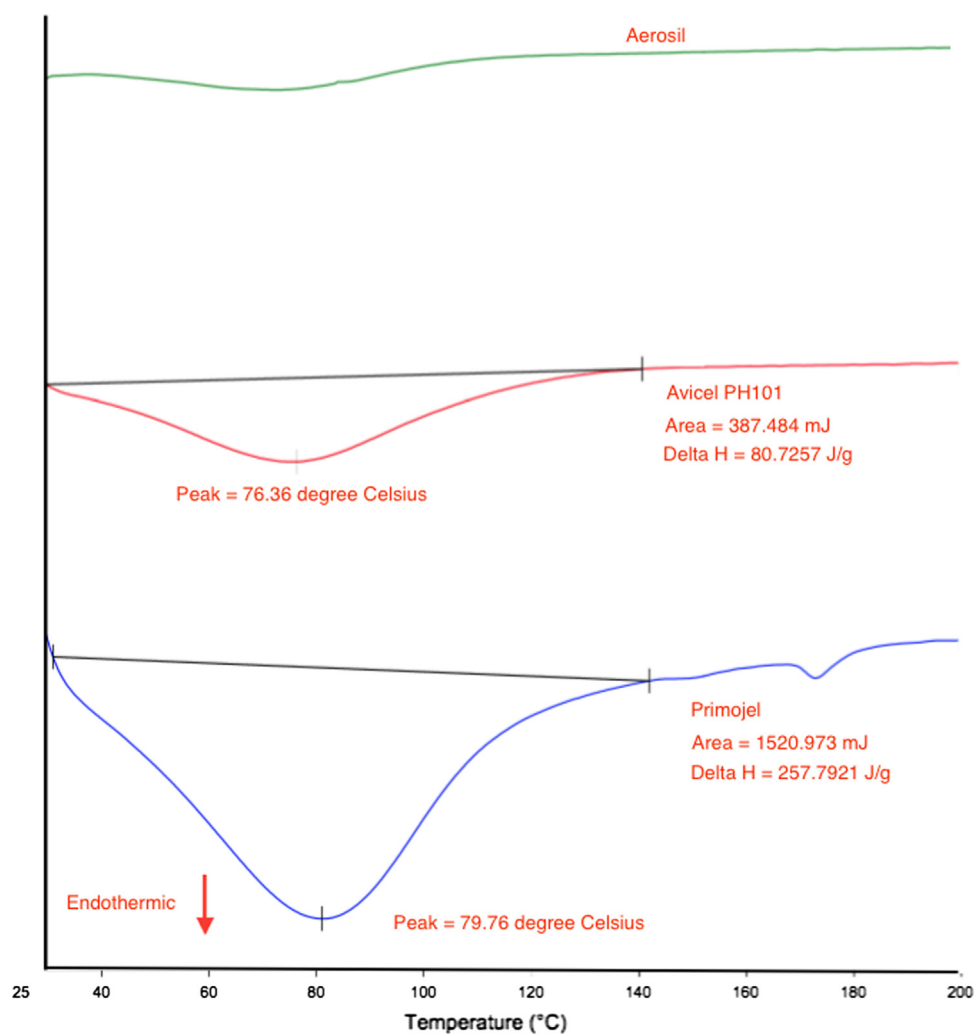


Fig. 7. DSC thermograms of excipients (aerosil, avicel PH101 and primojel).

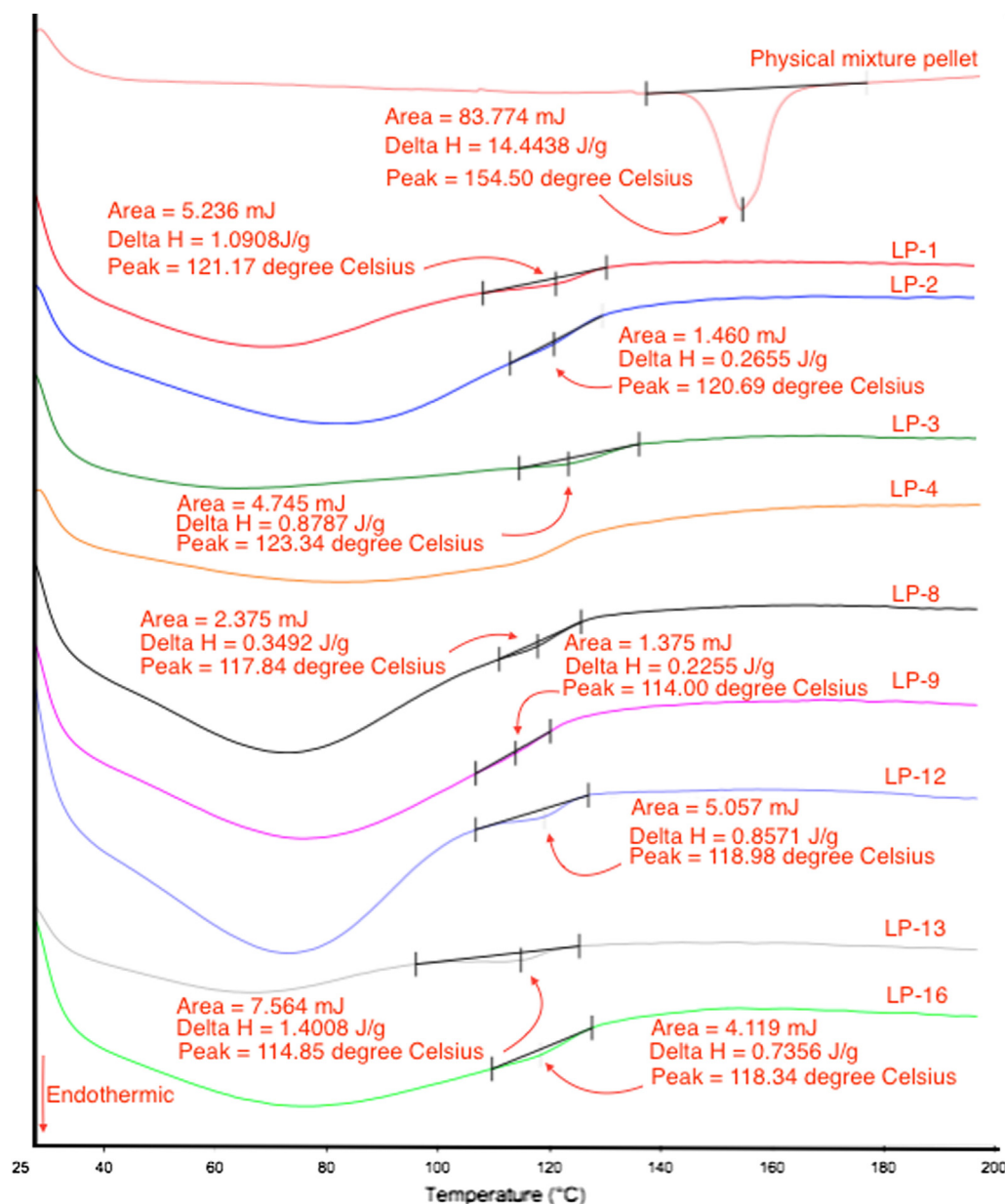


Fig. 8. DSC thermograms of physical mixture and all successful formulation.

sharp peaks (area and height) to estimate the crystallinity of each formulation. The relative crystallinity measured is with respect to AUC at 18.9° peak (Table 6). Note that the data does not represent the whole percentage of crystallinity of each formulation as only one crystalline peak is used for the analysis. The purpose of this study is to observe if the API crystallinity differs among each other; thus, using the AUC at 18.9° peak seems sufficient for the task. The results from the integrated peak area method show that all the Liqui-Pellet formulations (LP-4, LP-8, LP-9, LP-12, LP-13 and LP-16) have a slight reduction in the crystallinity in comparison to physical mixture pellet. This is expected as API are solubilized or held in a molecularly dispersed state in Liqui-Pellet formulation; hence, the crystallinity of API is reduced as indicated in the results. This reduction in the crystallinity of Liqui-Pellet formulations is not very remarkable as the concentration of drug in the formulations is very low compared to the other components of the formulation. The results from peak height method also show similar trend except for formulation LP-12, where it seems to be slightly

more crystalline than the physical mixture pellet. It should be noted that there are quite a few methods of measuring crystallinity via XRPD. This reflects the intricacy in obtaining accurate results.

3.8. DSC studies

The naproxen crystalline state is presented as a sharp endothermic peak ($T_m = 160.45^\circ\text{C}$ and $\Delta H = 64.23\text{ J/g}$), which is shown in Fig. 6. Thermograms of excipients are shown in Fig. 7; they display broad peaks for Avicel ($T_m = 76.36^\circ\text{C}$ and $\Delta H = 80.73\text{ J/g}$) and Primojel ($T_m = 79.76^\circ\text{C}$ and $\Delta H = 257.79\text{ J/g}$), which could be due to water evaporation within these hygroscopic excipients. Similar observations are seen from the authors' previous publications [2] and in Tiong and Elkordy work [42]. In contrast, Aerosil has not revealed any thermal transition at the heating range ($25\text{--}200^\circ\text{C}$) because of its amorphous nature and the T_g value being higher than the experimented range.

In comparing the naproxen and physical mixture pellet thermograms (Fig. 6 and Fig. 8), there is a slight shift of peak from 160.45 °C to 154.50 °C, respectively. This is likely caused by the influence of Avicel affecting the overall peak of naproxen in the physical mixture pellets. As temperature increases, API dissolves in the excipients, shifting the peak towards the left. Nonetheless, the crystalline state of naproxen is still present in the physical mixture pellet. This peak that indicates a crystalline state of naproxen becomes less prominent in the rest of the successful Liqui-Pellet formulations, implying that the Liqui-Pellet formulations crystallinity is reduced. This reduced crystallinity is due to the presence of naproxen in solubilized or molecularly dispersed state, which is supported by the enhanced drug dissolution rate of Liqui-Pellet formulations compared to physical mixture pellet.

4. Conclusion

Liqui-Pellet is a new and exciting technology; however, it is still in its infancy. The investigation of the amount of water and Tween 80 as parameters in Liqui-Pellet formulation clearly show that they have a crucial effect on the drug release profile. It can be seen that the combined effect of decreased water content and increased Tween 80 can significantly increase drug release rate i.e. by ≈25% (referring to LP-3 and LP-4 after 2 h). The reduction of water enhances drug release by reducing the cohesive strength of the Liqui-Pellet, which improves its disintegrating properties. The increase in Tween 80 concentration enhances drug release through increasing the proportion of drug being in solubilized or molecularly dispersed state. This increases the surface available for dissolution. In addition, Tween 80 reduces surface tension or cohesive force, which improves propensity for disintegration, contributing to the enhanced drug release rate. Despite reducing water and increasing Tween 80 contents resulting in faster drug release rate, there is a limit of how much water can be reduced and how much Tween 80 can be increased. Outside of this limit, the Liqui-Pellet formulation is likely to fail due to agglomeration. The fact that Liqui-Pellet drug release rate can be tailored by adjusting the mentioned parameters whilst maintaining excellent flow properties with a narrow size distribution. This is an indication of the flexibility in the formulation design of Liqui-Pellet which makes it a very valuable oral drug delivery system.

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